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ARTICLE

Rheumatic diseases and pregnancy

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Rheumatic diseases predominantly affect young women of childbearing age; therefore pregnancy is a topic of major interest. Pregnancy-induced changes in immune function can have an effect on underlying disease activity. Systemic lupus erythematosus (SLE), the most common autoimmune disease affecting women during their reproductive years, has an increased incidence of disease flares during pregnancy. In rheumatoid arthritis, on the other hand, there is spontaneous improvement in disease symptoms. However, rheumatic diseases and their treatment can have a significant impact on pregnancy outcomes. Poor pregnancy outcomes are largely associated with high disease activity. Pregnant women with rheumatic diseases constitute a high-risk population, with potential adverse fetal and maternal outcomes. Treatment options can be limited in pregnant women owing to concerns about the adverse effects of commonly used medication on the fetus. The aim of this article is to discuss the optimal management of pregnant women with SLE and other rheumatic diseases, including antiphospholipid antibody syndrome, Sjögren's syndrome, systemic sclerosis, rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. The effects of pregnancy on underlying diseases and *vice versa* are discussed.

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Systemic lupus erythematosus

Rheumatic diseases predominantly affect young women of childbearing age; therefore pregnancy is a topic of major interest. Pregnancy-induced changes in immune function can have an effect on underlying disease activity.^[1-3] Pregnant women with rheumatic diseases constitute a high-risk population, with potential adverse fetal and maternal outcomes. Treatment options can be limited in pregnant women owing to concerns about the adverse effects of commonly used medication on the fetus.^[4]

Systemic lupus erythematosus (SLE) is a multisystem disease and the most prevalent autoimmune disease affecting women during their reproductive years, with an incidence of 1/1 000 women.^[5] Women with SLE have normal fertility but may have complicated pregnancies.^[6] Prior exposure to cyclophosphamide is the main risk factor for infertility,^[5,6] and is related to dosing and age of the patient, with exposure for patients older than 35 years carrying a higher risk of premature ovarian failure.^[6]

Effects of pregnancy on systemic lupus erythematosus

The concern during pregnancy is the increased incidence of lupus flares. Measurable disease activity is thought to be present in 40 - 50% of pregnancies, with the most common manifestations being lupus nephritis, cutaneous disease, arthritis, and haematological disease, especially thrombocytopenia.^[2] About 75% of patients who flare during pregnancy will have lupus nephritis.^[2] Lupus flares occur throughout pregnancy but the rate seems higher during the third trimester and 3 months postpartum.^[6] Increased SLE disease activity is expected during pregnancy or in the postpartum period because of increased levels of oestrogen, prolactin and Th2 cytokines.^[2,7] Several studies have shown that the risk of flare during pregnancy is increased in women who have active disease in the 6 - 12 months before conception, in those who discontinue useful medications, in particular hydroxychloroquine, and in those with active lupus nephritis at conception or during the

previous 6 months.^[2,8] The latter is associated with an increased risk of progression to end-stage renal disease.^[2] All SLE patients should be counselled and evaluated before pregnancy. Women with active disease, who are not actively planning a pregnancy, or are taking drugs that are contraindicated during pregnancy, need reliable contraception.

Effects of systemic lupus erythematosus on pregnancy outcome

SLE patients have a 2 - 4-fold higher rate of pregnancy complications than an equivalent population without SLE.^[9] Pre-eclampsia occurs in about 23% of women with the disease, especially in those with co-existing antiphospholipid syndrome. This is approximately three times higher than the 7% occurrence rate in a population without the disease.^[9] Fetal loss (miscarriage or stillbirth) occurs in about 20% of pregnancies in women with SLE.^[6,8] While the risk of miscarriage is not significantly elevated, the risk of stillbirth is significantly higher compared with that in the general population.^[2] The increased risk of stillbirth is related to increased lupus activity and the presence of antiphospholipid antibodies.^[2,8] Patients with active lupus nephritis in the 6 months prior to conception or during pregnancy are at higher risk for pregnancy-related complications than SLE patients without renal disease, including spontaneous abortion, premature abortion, premature delivery, intrauterine growth restriction and pre-eclampsia.^[2] SLE patients with higher disease activity in combination with low complement levels or a positive anti-double-stranded DNA (dsDNA) have the highest rate of pregnancy loss and preterm birth.^[2] The most common fetal morbidity in SLE patients is prematurity and intrauterine growth retardation (IUGR), with preterm deliveries ranging between 17% and 49%.^[2] Lupus flare and pre-existing hypertension are the strongest predictors.

One of the major challenges is assessing a disease flare in pregnancy, as some of the physiological changes that may occur in pregnancy and pregnancy-related complications might mimic a lupus flare. Table 1 shows features that may help to diagnose a lupus flare.^[6]

Table 1. Features helpful for diagnosis of lupus flares in pregnancy

Unreliable features	Reliable features
Facial/palmar erythema	Palpable lupus rash
Alopecia	Synovitis
Arthralgia	Mucosal ulcers
Anaemia	Leucopenia (lymphopenia)
Thrombocytopenia	Red cells and/or casts in urine
Seizures	Rising anti-dsDNA
Hypertension	Reduced C3 and C4 ($\geq 25\%$)
Proteinuria	
Low C4	

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder defined by the occurrence of recurrent vascular (venous and arterial) thrombosis and pregnancy morbidity in the presence of persistently elevated antiphospholipid antibodies (aPL), anticardiolipin IgG/IgM, lupus anticoagulant and anti- $\beta 2$ -glycoprotein-1 IgG/IgM.^[1] APS affects women more commonly than men and is typically diagnosed between the ages of 30 and 40 years. APS can present alone (primary APS) or in the context of an underlying connective tissue disease (secondary APS). Patients with SLE will test positive for aPL in up to 65% of cases, but only about half of these will develop thrombosis and/or pregnancy morbidity (APS).^[1] One study revealed that APS was associated with SLE in 36% of cases.^[1]

Pregnancy and the first 6 weeks postpartum are known to be associated with a prothrombotic state with increased risk of developing deep vein thrombosis, pulmonary embolism and stroke.^[6] Venous thromboembolism is 2 - 4-fold more common in pregnancy after caesarean section than after vaginal delivery. Thrombotic complications are found in 1.7% of SLE pregnancies.^[9] Pregnancy in patients with APS represents an additional thrombotic risk.

Effects of antiphospholipid syndrome on pregnancy outcome

APS is one of the most important acquired causes of pregnancy loss.^[8] Women with aPL had an increased incidence of pregnancy loss after 10 weeks of gestation compared with an unselected obstetric population with 10 - 15% of pregnancy losses, which occurred mainly during the pre-embryonic (<6 weeks' gestation) or embryonic (6 - 9 weeks' gestation) period.^[1,8] The prevalence of aPL in the general obstetric patient is <2%; therefore universal screening cannot be justified.^[1] Women with a history of three or more first trimester pregnancy losses should be screened for aPL. All the above aPL should be measured to determine whether someone is aPL-negative. It is recommended that women with APS-related thrombosis be given prophylaxis during pregnancy, a combination of heparin (unfractionated or low molecular weight) and low-dose aspirin.^[10]

Several studies have reported pre-eclampsia in 20 - 50% of patients with APS, which usually manifests early and is severe.^[8] Beta-2 glycoprotein-1 has a predictive value for the occurrence of pre-eclampsia.^[1] The HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome has been reported in APS pregnancies and usually occurs earlier than in the general obstetric population (second trimester).^[11] Uteroplacental insufficiency has been noted to induce IUGR in 30% of APS patients, preterm delivery in 30%, and pre-eclampsia.^[1]

Sjögren's syndrome

Sjögren's syndrome is a chronic autoimmune inflammatory disease affecting primarily the exocrine glands, but also the extra-glandular structures. It can present alone (primary Sjögren's syndrome (pSS)) or be part of an underlying connective tissue disease, most commonly rheumatoid arthritis (RA) or SLE, and is then regarded as secondary Sjögren's syndrome.^[12]

pSS is 10 times more frequent in women than in men, with a peak incidence at or near menopause.^[1] Disease onset in pSS is when most patients have completed their families and therefore there is a paucity of data on pregnancy outcomes in this disease. Pregnancy, however, does not appear to have any effect on pSS as there are no major changes in symptoms.

Effects of primary Sjögren's syndrome on pregnancy outcome

Previous studies observed an increased rate in spontaneous abortions in women with pSS, but advanced maternal age of the first pregnancy could explain the increased impact of pregnancy complications.^[12] Results of a recent study indicate that women with pSS experience complicated pregnancies more frequently than controls, with an increased rate of preterm delivery, caesarean section and low-birth-weight infants.^[12] Patients with pSS are known to have a high prevalence of Ro/SSA and La/SSB antibodies but these can be present in other connective tissue diseases, particularly in SLE. Maternal transmission of IgG antibodies to the fetus usually occurs between weeks 16 and 32.^[6] Transmission of maternal Ro and La antibodies during pregnancy can cause neonatal lupus syndrome (NLS) in neonates, manifesting as transient cutaneous lupus lesions, cytopenia, hepatic and other systemic manifestations or complete heart block (CHB).^[1] CHB is the only permanent manifestation of NLS,^[1] with an estimated incidence of 1 - 2% and a 15 - 20% recurrence rate if the first child had CHB.^[1,2,7,8] Unfortunately there is no effective prophylactic therapy to prevent recurrence of CHB. The other clinical manifestations resolve within 4 - 6 months after birth.^[2] NLS can lead to death in 15 - 30% of cases owing to cardiac manifestations.^[7] About 67% of surviving affected children require permanent pacing before adulthood, the majority by the age of 1 year, and a third will need insertion of a pacemaker within the first 3 months of life.^[7]

Mothers with Ro and La antibodies should have their fetal heart rate assessed weekly and have serial echocardiograms from 16 weeks until about 25 weeks of gestation, and less frequently thereafter.^[7,8] The aim is to detect early fetal abnormalities that might precede CHB and offer intrauterine therapy to improve atrioventricular conduction speed.^[12] Maternal treatment with fluorinated steroids, e.g. dexamethasone, can reduce the antibody-mediated inflammatory damage of nodal tissue, but these drugs should not be used prophylactically in the absence of symptoms.^[8] Recent data suggest that hydroxychloroquine during pregnancy may reduce the incidence of congenital CHB in women with anti-Ro and anti-La antibodies.^[13]

Systemic sclerosis

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterised by fibrosis of the skin and internal organs, and pronounced alterations in the microvasculature. It predominantly affects women, with a peak age of onset around 40 - 50 years,^[1] leaving the potential to become pregnant after the onset of disease. It seems that pregnancy does not profoundly alter the disease. There may be aggravation of symptoms, in particular gastro-oesophageal reflux disease.^[6] Raynaud's phenomenon improves and cutaneous disease remains stable during pregnancy and postpartum.^[14]

Serious organ manifestations of SSc can threaten the outcome of pregnancy.^[1,14] The greatest risk in pregnancy to mother and fetus comes from a renal crisis, which can manifest as acute-onset hypertension or progressive renal failure and occur at any stage of pregnancy.^[6,14] Renal crisis can be difficult to distinguish from pre-eclampsia.^[6] Hypertensive disorders including pre-eclampsia have been found to be higher in SSc pregnancies, but the frequency of occurrence of renal crisis in pregnancy compared with non-pregnant SSc patients is similar.^[1] Risk factors for renal crisis are early diffuse SSc, rapidly progressing skin disease and high-dose steroids. Although angiotensin converting enzyme (ACE) inhibitors are not normally advised in pregnancy as they are associated with congenital abnormalities, they are essential to control hypertension and the associated renal crisis in pregnant patients with SSc.^[6,14] Another major risk factor is pulmonary hypertension (PHT). PHT poses a 30 - 50% maternal mortality risk in pregnancy^[15] and therefore a multidisciplinary team approach is required to manage these high-risk patients for a better pregnancy outcome. Preterm deliveries, IUGR and very-low-birth-weight infants are significantly more frequent in SSc than in healthy women, but the risk of miscarriage is the same.^[1]

Rheumatoid arthritis

RA is an autoimmune disease that results in a chronic, systemic inflammatory disorder that may affect many tissues, but principally affects synovial joints and can lead to significant joint destruction and disability. Women are two to three times more likely to develop RA than men, with an incidence of 1/2 000 during the childbearing years.^[5] In contrast to SLE, RA patients experience significant improvement in disease activity during pregnancy, with up to 75% of pregnant women experiencing improvement in their RA symptoms and over 50% improving during the first trimester.^[1,2] A small proportion of patients achieve complete remission. The trend is that disease activity continues to improve as gestation progresses and becomes most improved in the third trimester.^[16] Patients with high disease activity benefit the most. A recent study has shown that women who were negative for both rheumatoid factor and anticyclic citrullinated peptide – diagnostic antibody tests in RA – were more likely to improve in RA symptoms than those who were antibody-positive (75% v. 39%).^[17]

However, the majority of patients have recurrent disease, particularly in the initial 3 - 12 months postpartum, with up to 62% requiring increased drug therapy within the first 6 months postpartum.^[16]

The improvement in RA symptoms during pregnancy is thought to be due to the immunological changes associated with pregnancy, resulting in an increase in T helper 2 (Th2) cytokines, particularly interleukin 10 (IL-10), and the effects of hormonal changes.^[2,6,18] In addition, pregnancy promotes the development of regulatory T cells that suppress maternal autoimmune responses associated with the disease.^[2,6,18]

The increased risk of developing RA postpartum is thought to be related to the effects of prolactin, the levels of which are increased during lactation.^[2,6] Studies, however, have failed to demonstrate a correlation between a disease flare and breastfeeding.^[1]

It was previously thought that there was no risk to pregnancy outcome in women with RA, but a recent study found that there is a higher rate of lower mean birth weight and elective caesarean section than in healthy women.^[1] Another study showed that lower birth weight is independently correlated with disease activity.^[1]

Psoriatic arthritis

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis and has an equal gender distribution. Disease activity in PsA behaves in the same manner as in RA in articular disease, with up to 85% of patients improving during pregnancy.^[1] Pregnancy, however, does not have any effect on skin disease.^[1] Postpartum relapse occurs in 60 - 80% of patients 2 - 12 weeks postpartum. There is no evidence to support increased adverse pregnancy outcomes in women with PsA.

Ankylosing spondylitis

Ankylosing spondylitis (AS) is a chronic, systemic inflammatory disease affecting the axial skeleton, the entheses (sites of bony insertions of tendons and ligaments) and, occasionally, the peripheral joints. The hallmark of AS is inflammatory backache, and the disease predominantly affects men. There seems to be no improvement in symptoms during pregnancy in patients with AS.^[3] Previous studies show that disease activity remains high until early in the second trimester,^[3] with up to 70% of patients needing NSAIDs.^[1] Disease activity decreases in the third trimester, but complete remission is not achieved as in RA. Postpartum relapse occurs in 50 - 80% of AS patients within 4 - 12 weeks after delivery.^[1]

The rate of adverse pregnancy outcomes is the same as for healthy women; however, caesarean section is frequently performed in patients with AS. Ankylosis of the sacro-iliac joints, hip disease or total hip replacement does not preclude normal delivery.^[1]

Drug treatment during pregnancy

Adjustment of drug therapy in patients who are planning to become pregnant and those who are already pregnant is necessary to ensure that the underlying maternal disease is quiescent and that the drugs used are safe and compatible with embryonic and fetal development.^[19] Withdrawal of all drugs used prior to conception may result in a disease flare-up, which may be as catastrophic for pregnancy outcome as continuing with drugs that are harmful to the developing fetus.

Table 2 summarises the list of drugs that are safe and those that are contraindicated during pregnancy to treat rheumatic diseases.

Management of patients with anti-rheumatic diseases

Pregnancy in a woman with rheumatic diseases can have an increased risk of adverse maternal and fetal outcomes. Risks in the mother depend on disease activity before conception and throughout pregnancy, extent of organ involvement and presence of certain types of auto-antibodies.^[19] Risks for the fetus are related to maternal disease activity, presence of auto-antibodies and maternal therapy.^[19]

Women with rheumatic diseases who intend becoming pregnant should be provided with a preconception medical work-up that includes a complete clinical and laboratory assessment precisely reviewing risk factors and assessing the status of disease: anti-Ro and La, aPL, anti-dsDNA, complement level C3 and C4, kidney function, urinary protein, full blood count and inflammatory markers. The objective is to plan pregnancy during remission and withdraw medications that are not safe during pregnancy. An interdisciplinary team should manage high-risk patients.

All SLE patients should be on hydroxychloroquine, as it has been shown to prevent lupus flare-ups, have moderate protection against thrombosis and reduce development of CHB in children of mothers positive for Ro and La antibodies. Hydroxychloroquine should be continued in SLE patients and in those positive for Ro and

Table 2. Drug treatment during pregnancy^[1,4,6,19]

Drug	Contraindicated	Recommendations
Paracetamol	No	Safe throughout pregnancy
Codeine	No	Use with caution: respiratory distress and withdrawal syndrome
Non-steroidal anti-inflammatory drugs	No	Safe until 32 weeks' gestation: closure of ductus arteriosus
Aspirin	No	Use low dose
Steroids	No	Keep at ≤15 mg in 1st trimester
Chloroquine	No	Safe throughout pregnancy
Azathioprine	No	Safe throughout pregnancy
Cyclosporine	No	Safe throughout pregnancy
Salazopyrine	No	Safe throughout pregnancy
Tacrolimus	No	Safe throughout pregnancy
Methotrexate	Yes	Discontinue 3 months before conception
Leflunomide	Yes	Stop and wash out before pregnancy
Cyclophosphamide	Yes	Discontinue 3 months before conception, and pregnancy test before next infusion
Mycophenolate mofetil	Yes	Discontinue 6 weeks before conception
Abatacept	Yes	Discontinue 3 months before conception
Rituximab	Yes	Discontinue 6 - 12 months before conception
Tocilizumab	Yes	Discontinue 3 months before conception
Etanercept	Yes	Discontinue at missed period or after a positive pregnancy test
Certolizumab	No	Can be given throughout pregnancy: minimal passage to fetus
Monoclonal antibodies (adalimumab, infliximab, golimumab)	Yes	Discontinue at missed period or after a positive pregnancy test

La antibodies throughout pregnancy. APS patients should receive prophylaxis with low-dose aspirin in combination with heparin. ACE inhibitors are essential to control hypertensive renal crisis in systemic sclerosis, even in pregnancy. Patients with inflammatory arthritis who improve during pregnancy should be counselled for postpartum relapse and therapy planned accordingly.

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